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## Final Rule Webinar Series – 2 of 3

- The webinar will begin at 1 PM ET
- We will test the audio before we begin
  - All telephone lines are muted
- Use the Q & A panel to ask questions
  - Address questions to “All Panelists”
  - We will aim to address questions not answered today in the next webinar and/or with information on the ClinicalTrials.gov website
- After the webinar, submit questions to: [register@clinicaltrials.gov](mailto:register@clinicaltrials.gov)

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## Final Rule for Section 801 of the Food and Drug Administration Amendments Act of 2007 (42 CFR Part 11)

Final Rule Webinar Series – 2 of 3  
October 5, 2016

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National Library of Medicine

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## Webinar Series – Overview

- Webinar #1 (September 27, 2016) – now available online
  - Overview of the Final Rule
  - Effective Date and Compliance Date
- Webinar #2 (October 5, 2016)
  - Clinical Trial Registration Information and Update Requirements
- Webinar #3 (October 11, 2016 – please register)
  - Clinical Trial Results Information and Update Requirements
  - Quality Control Review Procedures and Posting

<https://clinicaltrials.gov/ct2/manage-recs/present#FinalRuleWebinar>

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## Today's Agenda

- A. Overview of Final Rule Requirements
- B. Clinical Trial Registration Information Submission Requirements
  1. Who must submit clinical trial registration information?
  2. Which applicable clinical trials must be registered?
  3. When must clinical trial registration information be submitted?
  4. What constitutes clinical trial registration information?
  5. When must clinical trial registration information be updated?

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## A. Overview of Final Rule Requirements

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The NEW ENGLAND JOURNAL of MEDICINE

### SPECIAL REPORT

#### Trial Reporting in ClinicalTrials.gov — The Final Rule

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H.,  
and Sarah Carr, B.A.

Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA) expanded the legal mandate for sponsors and others responsible for certain clinical trials of FDA-regulated drug, biologic, and device products to register their studies and report summary results information to ClinicalTrials.gov,<sup>1</sup> which is managed by the National Library of Medicine at the National Institutes of Health (NIH). The statute expanded registration requirements and provided a legally defined timeline with specific requirements for the systematic reporting of summary trial results. Although statutory components took effect before 2010, the FDAAA directed the Department of Health and Human Services (HHS) to issue regulations regarding certain statutory provisions and to consider possible expansion of the requirements through rule-making.

developed the final rule, which was made publicly available on September 16, 2016. Simultaneously, the NIH issued a complementary final policy, under which NIH-funded awardees and investigators will be expected to submit registration and results information for all NIH-funded clinical trials, whether or not the trials are covered by the FDAAA requirements.<sup>6</sup>

Here, we summarize and highlight key points about the final rule (see box).

#### BACKGROUND

The FDAAA established legal requirements for sponsors and designated principal investigators (i.e., responsible parties) to report specified clinical trial information for certain applicable clinical trials to ClinicalTrials.gov. In addition to registration, the statute established a system and man-

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## Regulatory Text - Table of Contents

### Subpart A – General Provisions

- § 11.2 - What is the purpose of this part?
- § 11.4 - To whom does this part apply?
- § 11.6 - What are the requirements for the submission of truthful information?
- § 11.8 - In what format must clinical trial information be submitted?
- § 11.10 - What definitions apply to this part?

### Subpart B – Registration

- § 11.20 - Who must submit clinical trial registration information?
- § 11.22 - Which applicable clinical trials must be registered?
- § 11.24 - When must clinical trial registration information be submitted?
- § 11.28 - What constitutes clinical trial registration information?
- § 11.35 - By when will the NIH Director post clinical trial registration information submitted under § 11.28?

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## Regulatory Text - Table of Contents (cont.)

### Subpart C – Results Information Submission

- § 11.40 - Who must submit clinical trial results information?
- § 11.42 - For which applicable clinical trials must clinical trial results information be submitted?
- § 11.44 - When must clinical trial results information be submitted for applicable clinical trials subject to § 11.42?
- § 11.48 - What constitutes clinical trial results information?
- § 11.52 - By when will the NIH Director post clinical trial results information submitted under § 11.48?
- § 11.54 - What are the procedures for requesting and obtaining a waiver of the requirements clinical trial results information submission?

### Subpart D – Additional Submissions of Clinical Trial Information

- § 11.60 - What requirements apply to the voluntary submission of clinical trial information for clinical trials of FDA-regulated drug products (including biological products) and device products?
- § 11.62 - What requirements apply to applicable clinical trials for which submission of clinical trial information has been determined by the NIH Director to be necessary to protect the public health?
- § 11.64 - When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?

### Subpart E – Potential Legal Consequences of Non-Compliance

- § 11.66 - What are potential legal consequences of not complying with the requirements of this part?

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## General Requirements (42 CFR Part 11)

- The responsible party for an applicable clinical trial (ACT) must:
  - **Register** the ACT on ClinicalTrials.gov no later than 21 days after enrollment of the first participant;
  - **Update** the ACT on ClinicalTrials.gov at least once every 12 months with some items requiring update within 15 or 30 days of a change (e.g., Recruitment Status, Primary Completion Date within 30 days)
  - **Submit summary results** (including adverse event information) not later than 1 year after the trial's Primary Completion Date, with delays allowed in some circumstances

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## B. Registration Submission Requirements

### 1. Who must submit clinical trial registration information?

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## Responsible Party

- 42 CFR 11.20 – Who must submit clinical trial registration information?
- 42 CFR 11.4 – To whom does this part apply?
  - Applies to a **responsible party** for an applicable clinical trial that is required to be registered under 42 CFR 11.22
  - Each applicable clinical trial or other clinical trial must have one (and only one) responsible party
  - The sponsor of the clinical trial will be considered the responsible party unless and until a principal investigator has been designated the responsible party

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## Determination of Sponsor

- Each applicable clinical trial must have one sponsor
  - (i) When an applicable clinical trial or other clinical trial is conducted under an investigational new drug application (IND) (or investigational device exemption (IDE), the IND or IDE holder will be considered the sponsor.
  - (ii) When an applicable clinical trial or other clinical trial is not conducted under an IND or IDE, the single person or entity who initiates the trial, by preparing and/or planning the trial, and who has authority and control over the trial, will be considered the sponsor.

## Designating Principal Investigator as the Responsible Party

- The sponsor may designate a principal investigator as the responsible party if such principal investigator meets all of the following requirements:
  - (A) Is responsible for conducting the trial;
  - (B) Has access to and control over the data from the trial;
  - (C) Has the right to publish the results of the trial; and
  - (D) Has the ability to meet all of the requirements for submitting and updating clinical trial information as specified in this part.

42 CFR 11.4(c)(2)

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## Designating Principal Investigator as the Responsible Party (cont.)

- A designation shall consist of
  - The sponsor obtaining from the principal investigator an acknowledgment of the principal investigator's responsibilities as responsible party, and
  - The principal investigator acknowledging the designation as responsible party in the format specified at <https://prsinfo.clinicaltrials.gov>.

42 CFR 11.4(c)(2)

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## Withdrawing Designation of Principal Investigator as the Responsible Party

- In the event that a principal investigator who has been designated the responsible party no longer meets or is no longer able to meet all the designation requirements
- The sponsor must withdraw the designation in the format specified at <https://prsinfo.clinicaltrials.gov>
- At which time the sponsor will be considered the responsible party unless and until the sponsor makes a new designation.

42 CFR 11.4(c)(3)

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## 2. Which applicable clinical trials must be registered?

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## Applicable Clinical Trial

- Defined in 42 CFR 11.10
- “Applicable drug clinical trial” and “applicable device clinical trial”, for example:
- Applicable Drug Clinical Trial means a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act ([21 U.S.C. 355](#)) or a biological product subject to section 351 of the Public Health Service Act ([42 U.S.C. 262](#)), where “clinical investigation” has the meaning given in [21 CFR 312.3](#) and “phase 1” has the meaning given in [21 CFR 312.21](#). A clinical trial of a combination product with a drug primary mode of action under [21 CFR part 3](#) is also an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part.

Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10 (see 81 FR 65009 – 16)

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## Determination of Applicable Clinical Trial Initiated On or After January 18, 2017

- Study Type = Interventional\*
- Studies a U.S. FDA Regulated Drug Product? OR Studies a U.S. FDA Regulated Device Product? = Yes [**new** data elements]
- Study Phase ≠ Phase 1 (drug and biological products) OR Primary Purpose ≠ Device feasibility (device products) [**new** menu option]
- Any of the following apply:
  - Facility Location: Country = U.S. (or U.S. territory)
  - U.S. FDA IND or IDE Number = Yes [not made public]
  - Product Manufactured in and Exported from the U.S. = Yes [**new** data element]

\* 42 CFR 11.22(b); If the study is a pediatric postmarket surveillance of a device product as required by FDA under Section 522 of the Federal Food, Drug, and Cosmetic Act, it meets the definition of an applicable device clinical trial  
IND = Investigational New Drug application; IDE = Investigational Device Exemption

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## Controlled (42 CFR 11.10(a))

- *Control or controlled* means, with respect to a clinical trial, that data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (*e.g.*, historical controls, including a human subject's own baseline data), as reflected in the pre-specified primary or secondary outcome measures. **For purposes of this part, all clinical trials with one or more arms and pre-specified outcome measure(s) are controlled.**

Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10 (see 81 FR 65020 – 21)

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## Study Type is Interventional

- *Interventional* means, with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes. (42 CFR 11.10(a) & 11.10(b)(7))
- Other Study Types: “Observational” and “Expanded Access”
  - Not applicable clinical trials (unless “observational” and a pediatric postmarket surveillance of a device product)
  - See also elaboration in Section IV.A.5 (81 FR 65037)

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## Studies a U.S. FDA Regulated Product

- *Studies a U.S. FDA-regulated Device Product* means that a clinical trial studies a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act. (42 CFR 11.10(b)(38))
- *Studies a U.S. FDA-regulated Drug Product* means a clinical trial studies a drug product (including a biological product) subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act. (42 CFR 11.10(b)(39))

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## Considerations for Studies a U.S. FDA-Regulated Drug Product

- Note: Similar elaborations apply for U.S. FDA-Regulated Device Product
- In determining whether a clinical trial studies a U.S. FDA-regulated drug product, a responsible party should consider whether
  - (a) the clinical trial is designed to examine the effect of the FDA-regulated drug product(s) or of differences in the intended use, including differences in dosing, frequency of use, or route of administration; and/or
  - (b) at least one of the pre-specified primary or secondary outcome measures reflects a characteristic or effect of the FDA-regulated drug product(s)

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## Considerations for Studies a U.S. FDA-Regulated Drug Product (cont.)

- Relationship to Intervention Type (42 CFR 11.10(b)(13))
  - A clinical trial for which the responsible party indicates the Intervention Type to be “dietary supplement” or “genetic” or “procedure” could in fact be an applicable drug clinical trial studying a drug product subject to section 505 of the FD&C Act or a biological product subject to section 351 of the PHS Act.
  - For example, a product otherwise marketed as a dietary supplement could be studied for the treatment of cancer, or a genetic trial could study a gene therapy.

Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10 (see 81 FR 65040 – 41)

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## Which applicable clinical trials must be registered? (42 CFR 11.22)

- Any **applicable clinical trial** that is
  - Initiated after September 27, 2007, or
  - Initiated on or before September 27, 2007, with Primary Completion Date after December 26, 2007 (i.e., ongoing study)
- Determining the **date of initiation**
  - On the date on which the first human subject is enrolled
  - Initiation is the “Study Start Date” data element

42 CFR 11.22(a)

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### 3. When must clinical trial registration information be submitted?

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### When must clinical trial registration information be submitted? (42 CFR 11.24)

- Generally 21 calendar days after the first human subject is enrolled (i.e., actual Study Start Date)
- Enroll or Enrolled definition (42 CFR 11.10(a))
  - “A human subject’s, or their legally authorized representative’s, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR Part 50 and/or 45 CFR Part 46 (or any successor regulation(s)), as applicable.”
  - “For the purposes of this part, potential subjects who are screened for the purpose of determining eligibility for the trial, but do not participate in the trial, are not considered enrolled unless otherwise specified by the protocol.”

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## 4. What constitutes clinical trial registration information?

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## What constitutes clinical trial registration information? (42 CFR 11.28)

- 42 CFR 11.28(a)(1) indicates ACTs initiated before January 18, 2017 follow the requirements in the statute
- 42 CFR 11.28(a)(2) lists the data elements to be submitted for ACTs initiated on or after January 18, 2017
  - (i) Descriptive information
  - (ii) Recruitment information
  - (iii) Location and contact information
  - (iv) Administrative data
- See also “Changes from Current Practice Described in the Final Rule” (<https://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf>)

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## Which Requirements Apply? Final Rule v. Statute

- **Registration information** determined by Study Start Date
  - Study Start Date on or after January 18, 2017: FINAL RULE
  - Study Start Date before January 18, 2017: STATUTE (FDAAA)
    - Study Start Date after September 27, 2007 but before January 18, 2017
    - Study Start Date on or before September 27, 2007, with Primary Completion Date after December 26, 2007 (i.e., ongoing study)
- Protocol Registration and Results System (PRS) will rely on Study Start Date to determine which registration information requirements apply

Final Rule, Section IV.F. Table on Applicability of Requirements in 42 CFR 11

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## Overview of PRS Implementation Plans

- By Late November: Targeting release to PRSTest with the registration and results final rule data elements
  - Data element definition documents and XML schema will be available
  - For informational purposes; do not use PRSTest as a “staging area” for PRS
- January 18, 2017: Effective Date
  - Release will be operational on PRS; registration data elements newly required by the final rule will be available and have a WARNING if not completed (only if Study Start Date  $\geq$  Jan 18, 2017)
- April 18, 2017: Compliance Date
  - Registration data elements newly required by the final rule will have ERRORS if not completed (only if Study Start Date  $\geq$  Jan 18, 2017)

PRS Test: <https://prstest.nlm.nih.gov>

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## Descriptive Information

- Brief Title (including Acronym)
- Official Title \*
- Brief Summary
- Primary Purpose \*
  - Device feasibility (new option); used to determine if not ACT
- Study Phase (clinical trial of a drug)
  - Phase 0 not listed; meets definition of Phase 1
- Study Type
- Study Design \* (all sub-elements)
  - Interventional Study Model
    - Sequential (new option)
  - Number of Arms
  - Arm Information
    - Arm Type, Arm Title, Arm Description
  - Allocation
  - Masking
    - Identify roles (e.g., investigator) that are masked or specify “no masking”
    - Specification of open, single blind, double blind no longer required

\* Newly required by the final rule

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## Descriptive Information (cont.)

- Pediatric Postmarket Surveillance of a Device Product \* (new)
- Primary Disease or Conditions Being Studied in the Trial, or the Focus of the Study
- Intervention Information
  - Intervention Name(s)
  - Other Intervention Name(s), if any \*
  - Intervention Description \*
  - Intervention Type
- Study Start Date \*
  - Day, month, year when actual
- Primary Completion Date
- Study Completion Date \*
- Enrollment \*

\* Newly required by the final rule

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## Descriptive Information (cont.)

- Studies a U.S. FDA-regulated Device Product \* (new)
- Studies a U.S. FDA-regulated Drug Product \* (new)
- Device Product Not Approved or Cleared by U.S. FDA \*
  - [comparable to current Delayed Posting data element]
- Post Prior to U.S. FDA Approval or Clearance (new optional)
- Product Manufactured in and Exported from the U.S. \* (new)
- Primary Outcome Measure Information
  - Name, Description \*, Time Frame
- Secondary Outcome Measure Information
  - Name, Description \*, Time Frame

\* Newly required by the final rule

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## Outcome Measure Information

- Each primary and secondary outcome measure must be submitted
- Definitions (42 CFR 11.10(a))
  - Primary Outcome Measure
    - Outcome measures of greatest importance specified in the protocol, usually the one(s) used in the power calculation
  - Secondary Outcome Measure
    - Outcome measure of lesser importance than primary outcome
    - Part of pre-specified analysis plan
    - Not specified as exploratory or other
- Outcome Measures Include:
  - Name of the specific measure (e.g., systolic blood pressure)
  - Description of the metric used to characterize the specific outcome measure (e.g., mean value of systolic blood pressure)
  - Time point(s) at which the measurement is assessed for the specific metric used (e.g., 24 weeks after initiation of treatment)
    - A single attribute assessed at multiple points in time, is considered different outcome measures
    - Systolic blood pressure at 3, 6 and 12 months is three different outcomes

Section IV.B.4. What constitutes clinical trial registration information? - §11.28 (81 FR 65046)

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## Recruitment Information

- Eligibility Criteria
- Sex/Gender
  - Sex and, if applicable, gender
- Age Limits
- Accepts Healthy Volunteers \*
- Overall Recruitment Status
  - Why Study Stopped (if terminated, withdrawn, suspended) \*
- Individual Site Status
- Sex: A person's classification as male or female based on biological distinctions
  - Specify: male, female, or all
- Gender: A person's self-representation of gender identity
  - If applicable, specify if study eligibility is based on gender
  - Additional free-text element to provide descriptive information

\* Newly required by the final rule

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## Recruitment Information (cont.)

- Availability of Expanded Access \*
  - Responsible Party is both the manufacturer and sponsor of ACT
  - Must indicate whether there is expanded access to the investigational drug product under FDA regulations:
    - For individual patients (including emergency use)
    - For intermediate-size patient populations
    - Under a treatment IND or protocol
  - Must also provide NCT number of expanded access record, when available
- Note: Requirements for Expanded Access Record described in 42 CFR 11.28(c)
  - Similar categories as in 42 CFR 11.28(a), but limited set of data elements based on relevance
  - Expanded Access Type \* (new)
    - Individual patient
    - Intermediate
    - Treatment use
  - Fewer data elements required when only "individual patient" expanded access

\* Newly required by the final rule

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## Location and Contact Information

- Location and Contact Information
  - Name of the Sponsor
  - Responsible Party, by Official Title
    - Sponsor, Sponsor-Investigator, or Principal Investigator
  - Facility Information
    - Name, Location, Contact or Central Contact

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## Administrative Data

- Unique Protocol Identification Number
- Secondary ID (and ID Type) \*
- U.S. FDA IND or IDE Number (not public)
  - Center, Number, Sequence
- Record Verification Date
- Human Subjects Review Board Status (will be public)
- Responsible Party Contact Information \* (new - not public)

\* Newly required by the final rule

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## 5. When must clinical trial registration information be updated?

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### Updates – Registration Information (42 CFR 11.64(a)(1))

- For trials initiated before January 18, 2017 (FDAAA)
  - In general, must be updated at least **once per year**
  - **30 calendar day updates**
    - Overall Recruitment Status not later than 30 calendar days after any change
    - Primary Completion Date (PCD) not later than 30 calendar days after the clinical trial reaches the actual PCD
- For trials initiated on or after January 18, 2017 (Final Rule)
  - In general, must be updated at least **once per year**
  - **15 calendar day update**
    - Device Product Not Approved or Cleared by U.S. FDA must be updated not later than 15 calendar days after a change in approval or clearance status
  - **30 calendar day updates** for other elements (next slides)

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## 30 Day Updates – Registration Information

- Study Start Date (after first human subject is enrolled)
- Intervention Name (after establishment of a non-proprietary name)
- Availability of Expanded Access (after becomes available, including NCT number)
- Expanded Access Record (after any change in status and type)
- Overall Recruitment Status (after any change in status)
  - If changed to “suspended”; “terminated”; or “withdrawn”; then also must submit Why Study Stopped data element
- Individual Site Status (after a change in status for any individual site)
- Human Subjects Protection Review Board Status (for any status change)
- Primary Completion Date (after the trial reaches its actual PCD)
  - Date is changed to “actual”
  - Enrollment data element specifying actual number of participants must be submitted
- Study Completion Date (after the trial reaches its actual SCD)
- Responsible Party, by Official Title (after change in RP or official title)
- Responsible Party Contact Information (after change in RP or contact information)

42 CFR 11.64(a)(1)

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## Updates – Registration Information (cont.)

- Other Update Requirements
  - Record Verification Date
    - Any time responsible party reviews 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
  - Protocol amendments that impact registration information
    - If protocol amended with changes communicated to human subjects, then any relevant clinical trial registration information must be submitted not later than **30 calendar days** after the protocol amendment is approved by a human subjects protection review board

42 CFR 11.64(a)(1)

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## Updates – Registration Information (cont.)

- Additional Update Requirements with Results Submission
  - Registration information must also be updated at the time that results information is initially submitted
  - Registration information is still based on when the trial initiated
    - For clinical trials initiated before January 18, 2017: STATUTE (FDAAA)
    - For clinical trials initiated on or after January 18, 2017: Final Rule

42 CFR 11.64(a)(1)

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## Additional Resources

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<https://clinicaltrials.gov/ct2/manage-recs/present#FinalRuleWebinar>

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## NIH Resources

- NIH News Release on the HHS Final Rule and NIH Policy
  - <https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public>
- NIH Policy on the Dissemination of Clinical Trial Information
  - NIH Guide Notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html>
  - Questions: [clinicaltrials.disseminationpolicy@mail.nih.gov](mailto:clinicaltrials.disseminationpolicy@mail.nih.gov)

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## ClinicalTrials.gov Resources

- Submit Studies: <https://clinicaltrials.gov/ct2/manage-recs>
  - FDAAA 801 Requirements – Regulations Implementing FDAAA 801
    - Changes from Current Practice Described in the Final Rule (PDF)
      - <http://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf>
    - Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. *N Engl J Med*; 2016. DOI: 10.1056/NEJMSr1611785.
      - <http://www.nejm.org/doi/full/10.1056/NEJMSr1611785>
  - Training Materials – Final Rule Webinar Series (will be archived)
- Final Rule Information: <https://prsinfo.clinicaltrials.gov>
- Questions: [register@clinicaltrials.gov](mailto:register@clinicaltrials.gov)