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Final Rule Webinar Series – 3 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



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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 – 3 of 3
October 11, 2016

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National Library of Medicine



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<https://ClinicalTrials.gov>

3. When must clinical trial results information be submitted?

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When must clinical trial results information be submitted for applicable clinical trials?

- Standard submission deadline (42 CFR 11.44(a))
 - Applies to applicable clinical trials required to have results information submitted under 42 CFR 11.42
 - Results information must be submitted no later than 1 year after the Primary Completion Date
- Delayed submission
 - Seeking approval, licensure, or clearance of a **new use** (42 CFR 11.44(b))
 - Seeking **initial** approval, licensure, or clearance (42 CFR 11.44(c))
 - Extensions for good cause (42 CFR 11.44(e))

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Submitting Partial Results Information (42 CFR 11.44(d))

- Addresses situations in which secondary outcome measure(s) or additional adverse event information are not collected by the primary completion date
 - Secondary outcome measure (SOM) is due no later than one year after the date on which the final subject is examined or receives an intervention for purposes of final collection of data for that SOM
 - Additional adverse event information is due no later than one year after the date of data collection of that information
 - If certification delaying results information is submitted under 42 CFR 11.44(b) or (c), then later of due dates

Final Rule Section IV.C.3. When must results information be submitted for applicable clinical trials subject to § 11.42? § 11.44 (81 FR 65066 – 79)

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Submitting Partial Results Information (42 CFR 11.44(d))

- Study Completion Date (42 CFR 11.10(a))
 - “Date the final subject was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (e.g., last subject’s last visit), whether the clinical trial concluded according to the pre-specified protocol or was terminated”
 - Helps identify requirements for clinical trial results information and when obligations for updates and corrections are fulfilled
- Responsible party may need to submit partial results information several times
- Obligation to submit results continues until all required results information is submitted – i.e., not later than 1 year following Study Completion Date

Final Rule Section IV.C.3. When must results information be submitted for applicable clinical trials subject to § 11.42? § 11.44 (81 FR 65066 – 79)

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4. What constitutes clinical trial results information?

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What constitutes clinical trial results information? (42 CFR 11.48)

- 42 CFR 11.48(a) applies to applicable clinical trials required to register* and with a Primary Completion Date on or after January 18, 2017 (effective date)
- Results information consists of:
 - (1) Participant Flow
 - (2) Demographic and baseline characteristics
 - (3) Outcomes and statistical analyses
 - (4) Adverse event information
 - (5) Protocol and statistical analysis plan
 - (6) Administrative information
 - (7) Additional clinical trial results information for applicable device clinical trials of unapproved or uncleared device products
- See also “Changes from Current Practice Described in the Final Rule” (<https://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf>)

* Other than a pediatric postmarket surveillance of a device product that is not a clinical trial (see 42 CFR 11.48(b))

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Which Requirements Apply? Final Rule v. Statute

- **Results information** determined by Primary Completion Date
 - Primary Completion Date on or after January 18, 2017: FINAL RULE
 - Primary Completion Date before January 18, 2017: STATUTE (FDAAA)
- Protocol Registration and Results System (PRS) will rely on Primary Completion Date (PCD) to determine which results information requirements apply
- Although we intend to make most results data elements specified in 42 CFR 11.48(a) available in PRS on January 18, 2017, the earliest results information would be due under final rule requirements is January 18, **2018**

Final Rule, Section IV.F. Table on Applicability of Requirements in 42 CFR Part 11 (81 FR 65121)

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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 (except protocols)
 - Data element definition documents and XML schema will be available (new data elements will be additive; intend for “old” XML schema to work indefinitely)
 - For informational purposes; do not use PRSTest as a “staging area” for PRS
- January 18, 2017: Effective Date
 - Release will be operational on PRS; results data elements newly required by final rule will be available and have WARNING if not completed (if PCD \geq Jan 18, 2017)
- April 18, 2017: Compliance Date
 - Results data elements newly required by final rule will have ERRORS if not completed (if PCD \geq Jan 18, 2017)

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

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Participant Flow (42 CFR 11.48(a)(1))

- Participant Flow Arm Information (Title and Description *)
- Pre-Assignment Information, if any *
 - Significant events that occur after enrollment and prior to assignment to an arm
- Participant Data
 - Number of human subjects that started and completed the clinical trial, by arm
 - If assignment is based on a unit other than participants, also include a description of the unit of assignment (e.g., eyes, lesions, implants) and number of units that started and completed the clinical trial, by arm * (new)

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65079 - 81)

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Demographic and Baseline Characteristics (42 CFR 11.48(a)(2))

- Baseline Characteristics Arm/Group Information (Title and Description *)
- Baseline Analysis Population Information
 - Overall Number of Baseline Participants
 - Overall Number of Units Analyzed * (new)
 - 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 *
 - If the Overall Number of Baseline Participants (or units) differs from the number of human subjects (or units) assigned to the arm

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65081 - 84)

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Demographic and Baseline Characteristics

- Baseline Measure Information
 - Age
 - Sex/Gender
 - Race and Ethnicity * (if collected under protocol)
 - Other measure(s) that were assessed at baseline and used in the analysis of the primary outcome measure(s) *

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65081 - 84)

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Demographic and Baseline Characteristics (cont.)

- Baseline Measure Information
 - Name and Description of Measure, including any categories used to submit Baseline Measure Data
 - Measure Type and Measure of Dispersion
 - Added “count of participants”, “count of units,” and “geometric least squares mean” to Measure Type options (**new**)
 - Removed “log mean” as Measure Type option
 - Unit of Measure
- Baseline Measure Data
 - Additional option for specifying when data are mutually exclusive and exhaustive
- Number of Baseline Participants (and Units) * (**new**)
 - If different from Overall Number of Baseline Participants or Overall Number of Units Analyzed

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65081 - 84)

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Outcomes and Statistical Analyses (42 CFR 11.48(a)(3))

- For each primary and secondary outcome measure
- Outcome Measure Arm/Group Information (Title and Description *)
- Analysis Population Information
 - Number of Participants Analyzed
 - Number of Units Analyzed
 - If the analysis is based on a unit other than participants, a description of the unit of analysis (e.g., eyes, lesions, implants)
 - Analysis Population Description *
 - If Number of Participants Analyzed or Number of Units Analyzed differs from number of human subjects or units assigned to the arm

* Newly required by the final rule

Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65081 - 84)

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Outcomes and Statistical Analyses

- Outcome Measure Information
 - Name of the specific outcome measure, including any categories in which Outcome Measure Data are aggregated
 - Description of metric used to characterize specific outcome measure *
 - Time point(s) at which the measurement was assessed
 - Outcome Measure Type (Primary, secondary, other pre-specified, post hoc)
 - Measure Type and Measure of Dispersion or Precision
 - Same modifications as described for similar elements in baseline
 - Unit of Measure
- Outcome Measure Data

* Newly required by the final rule

Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65084 - 90)

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Outcomes and Statistical Analyses (cont.)

- Result(s) of scientifically appropriate tests of statistical significance of primary and secondary outcome measures (limited to statistical analyses that rely on submitted outcome measure data)
 - Pre-specified in the protocol and/or statistical analysis plan and performed on the outcome measure data (excludes statistical analyses considered exploratory)
 - Made public by the sponsor or responsible party prior to the date on which clinical trial results information is submitted for the primary outcome measure(s)
 - Conducted on a primary outcome measure in response to a request by FDA prior to the date on which clinical trial results information is submitted for the primary outcome measure(s)
- Does not reflect Agency's agreement that analyses are necessarily valid

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65084 - 90)

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Statistical Analyses

- Statistical Analysis Overview, including
 - Identification of arms compared
 - Type of statistical test conducted
 - Superiority, non-inferiority, equivalence, or other (appropriate for single-group or other descriptive statistics) (new)
 - For a non-inferiority or equivalence test, a description that includes the power calculation and non-inferiority or equivalence margin
- One of the following, as applicable
 - Statistical Test of Hypothesis (p-value and procedure used)
 - Method of Estimation (estimation parameter, estimated value, and confidence interval (if calculated))
 - General "other" option if information can't be submitted using above options

Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65084 - 90)

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Considerations for Terminated Trials

- Trial terminated before data are collected for primary and/or secondary outcome(s)
 - Specify zero (“0”) for Number of Participants Analyzed
 - Outcome Measure Data not required to be submitted
 - Must still provide Participant flow, Demographic and baseline characteristics, and Adverse event information
- Outcome measure data collected, but actual enrollment falls well below target
 - Outcome measure information and data must be submitted
 - Statistical analysis information not expected to be submitted
 - If privacy considerations; 42 CFR 11.54 (waiver) may apply
 - Expected to be requested and granted in only a very limited number of situations

Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65084 - 90)

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Adverse Event Information (42 CFR 11.48(a)(4))

- Information for completing three tables summarizing anticipated and unanticipated adverse events collected by arm or comparison group
 - (1) All serious adverse events
 - (2) Adverse events, other than serious adverse events, that exceed a frequency of 5 percent within any arm of the clinical trial
 - (3) All-cause mortality * (new)

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65090 - 97)

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Adverse Event Information

- Methods for collecting adverse events
 - Time Frame *
 - Adverse Event Reporting Description *
 - If adverse event information collected in the clinical trial is collected based on a different definition of adverse event and/or serious adverse event
 - Collection Approach *
 - The type of approach taken to collect adverse event information, whether systematic or non-systematic

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65090 - 97)

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Adverse Event Information (cont.)

- Information for each of the three tables
 - Adverse Event Arm/Group Information (Title and Description *)
 - Total Number (participants) Affected, by arm or comparison group (new; all-cause mortality *)
 - Total Number (participants) at Risk, by arm or comparison group (new; all-cause mortality *)
- Adverse Event Information for each table (except all-cause mortality)
 - Descriptive term for the adverse event
 - Organ system associated with the adverse event
 - Added “Product issues” to list of options (new)
- Adverse Event Data for each table (except all-cause mortality)
 - Number of human subjects affected by adverse event
 - Number of human subjects at risk for adverse event (if different from total)

* Newly required by the final rule
Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65090 - 97)

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Protocol and Statistical Analysis Plan (42 CFR 11.48(a)(5))

- A copy of the protocol and statistical analysis plan (if not included in the protocol) * (new)
 - Including all amendments approved by human subjects review board (if applicable) before time of submission that apply to all locations
 - Cover page with Official Title, NCT number, and date of document
 - May redact:
 - Names, addresses, and other personally identifiable information
 - Trade secret and/or confidential commercial information (unless otherwise required to be submitted under this part)
 - Common electronic document format specified at <https://prsinfo.clinicaltrials.gov>

* Newly required by the final rule
Final Rule Section III.D. Submission of Protocols and Statistical Analysis Plans (81 FR 64999 - 65002)

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Administrative Information (42 CFR 11.48(a)(6))

- Results Point of Contact
 - Name or official title of the point of contact
 - Name of the affiliated organization
 - Telephone number and email address of the point of contact
- Certain Agreements
 - An indication of whether the principal investigator (PI) is an employee of the sponsor and, if not,
 - Whether there is any agreement between the sponsor (or its agent) and the PI restricting the PI's ability, after the PCD, to discuss publicly or publish the clinical trial results
 - Excludes agreements solely to comply with laws protecting the privacy of human subjects participating in the clinical trial

Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65097 - 99)

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5. When must clinical trial results information be updated?

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When must clinical trial results information submitted to ClinicalTrials.gov be updated? (42 CFR 11.64(a)(2))

- For trials with a Primary Completion Date on or after January 18, 2017 (i.e., subject to 42 CFR 11.48)
- In general, clinical trial results information must be updated at least **once per year**, except for the protocol and statistical analysis plan and certain agreements

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C. Posting and Quality Control Review Procedures

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Posting of Clinical Trial Registration Information

- Applicable drug clinical trials (42 CFR 11.35(a))
 - Post not later than 30 calendar days after the responsible party has submitted registration information (excludes certain admin. data)
- Applicable device clinical trials (42 CFR 11.35(b))
 - Device product previously approved or cleared
 - Post as soon as practicable but not later than 30 calendar days after clinical trial results information is required to be posted, as specified in 42 CFR 11.52
 - Device product that has not been previously approved or cleared
 - Post not earlier than the date of FDA approval or clearance of the device product (“lockbox”) and not later than 30 calendar days after the date of that approval or clearance, unless responsible party authorizes posting (“opt-out”)

Posting of Clinical Trial Results Information

- By when will the NIH director post clinical trial results information? (42 CFR 11.52)
 - Post not later than 30 calendar days after the responsible party submits the information

Final Rule Section IV.C.5. By when will the NIH Director post submitted clinical trial results information? § 11.52 (81 FR 65101)

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Posting and Quality Control

- Intend to continue a form of quality control (QC) review at time of submission that is similar to procedures we have been using
 - (1) automated system-based check; (2) manual review
- Interpret the statutory posting deadline to be a clearly delineated timeline between submission and posting
 - Information will be posted even if QC review process has not concluded
 - Registration will not receive NCT number until QC review process has concluded
 - Posted record will contain information to make clear process has not concluded
 - Will evaluate ways posted record could specify data element(s) that may contain errors, deficiencies, and/or inconsistencies

Final Rule Section IV.B.5. (81 FR 65062 – 63), Final Rule Section IV.C.5. (81 FR 65101), Final Rule Section IV.D.3. (81 FR 65108 - 17)

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Quality Control (42 CFR 11.64(b)(1))

- Director will establish procedures for quality control review specified at <https://prsinfo.clinicaltrials.gov>
- Director may provide electronic notification to the responsible party of apparent errors, deficiencies and/or inconsistencies that are identified by quality control review
- The responsible party must correct or address all apparent errors, deficiencies, and/or inconsistencies
 - Within 15 calendar days for clinical trial registration information
 - Within 25 calendar days for clinical trial results information

Final Rule Section IV.D.3. When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected? § 11.64 (81 FR 65108 - 17)

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Other Corrections (42 CFR 11.64(b)(2))

- A responsible party who becomes aware of errors (other than those identified in the quality control process), shall correct or address such errors
 - Within 15 days for clinical trial registration information
 - Within 25 days for clinical trial results information

Final Rule Section IV.D.3. When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected? (81 FR 65108 - 17)

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When Obligation to Submit Updates Ends (42 CFR 11.64(a)(3))

- If clinical trial results information is required to be submitted, obligation to update clinical trial information ends when:
 - All required clinical trial results information has been submitted; and
 - Corrections have been made or addressed in response to any notice received in the quality control process under 42 CFR 11.64(b)(1).
- If no clinical trial results information is required to be submitted, obligation to update clinical trial registration information ends when:
 - All required clinical trial registration information has been submitted; and
 - Corrections have been made or addressed in response to any notice received in the quality control process under 42 CFR 11.64(b)(1).

Final Rule Section IV.D.3. When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected? (81 FR 65108 - 17)

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When Obligation to Correct Ends (42 CFR 11.64(b)(2)(ii))

- Obligation to correct or address errors a responsible party becomes aware of (42 CFR 11.64(b)(2))
- If clinical trial results information is required to be submitted:
 - All required clinical trial results information has been submitted; and
 - Corrections have been made or addressed in response to any notice received in the quality control process under 42 CFR 11.64(b)(1)
- If no clinical trial results information is required to be submitted:
 - All required clinical trial registration information has been submitted; and
 - Corrections have been made or addressed in response to any notice received in the quality control process under 42 CFR 11.64(b)(1).

Final Rule Section IV.D.3. When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected? (81 FR 65108 - 17)

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Additional Resources

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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

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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