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Final Rule Special Topics

Clinical Trials Registration Taskforce
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https://ClinicalTrials.gov

Final Rule Topics

- Applicable Clinical Trial Determination Checklist
- Expanded Access
- Protocol and Statistical Analysis Plan
- Certify Initial Approval
- PRS Implementation

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Applicable Clinical Trial

- **Defined in 42 CFR 11.10**
- **Applicable Device Clinical Trial**
  - A prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes);
  - A pediatric postmarket surveillance of a device product as required under section 522 of the Federal Food, Drug, and Cosmetic Act; or
  - A clinical trial of a combination product with a device primary mode of action under 21 CFR part 3, is an applicable device clinical trial, provided that it meets all other criteria of the definition under this part.
- **Applicable Drug Clinical Trial**
  - 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 or a biological product subject to section 351 of the Public Health Service Act

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

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
  - Product Manufactured in and Exported from the U.S. = Yes [new 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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Checklist-based Tool for ACT Determination

- In order to assist users in evaluating, prior to beginning the registration process, whether their clinical trial or study is an applicable clinical trial and potentially subject to the requirements of the statute and the final rule, a checklist-based tool will be made available at *https://prsinfo.clinicaltrials.gov* (or successor site) for sponsors and others before the effective date of the rule. Tool will be external to the ClinicalTrials.gov PRS and separate from the registration process
- Outcome generated by the checklist tool will not be retained by the Agency and will not be binding on either the user or any government Agency in any future actions

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Final Rule Section IV.B.2. Which applicable clinical trials must be registered? - § 11.22 (81 FR 65030 -32)

Checklist-based Tool – Additional Elaboration

- Responsible parties or other users who use the checklist tool are responsible for using accurate data about a clinical trial or study and for conducting the evaluation.
- The Agency believes that this data element-based approach provides an objective, transparent set of criteria for responsible parties and other users to evaluate, prior to registering a trial, whether a clinical trial or study is an applicable clinical trial and for such users of *ClinicalTrials.gov* to understand the data elements used in evaluating whether a clinical trial or study is an applicable clinical trial.
- Once clinical trial registration information has been submitted, the Agency will be able to identify applicable clinical trials based on the set of data elements identified in 42 CFR 11.22(b).
- We did not receive any specific examples, as invited, of situations in which the proposed approach would misidentify an applicable clinical trial.

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Final Rule Section IV.B.2. Which applicable clinical trials must be registered? - § 11.22 (81 FR 65030 -32)

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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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)

Final Rule Section IV.B.4. What constitutes clinical trial registration information? - § 11.28 (81 FR 65032 - 62)

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Recruitment Information & Expanded Access

- Availability of Expanded Access *
  - Responsible Party is both the manufacturer of the investigational drug product and the sponsor of the 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
- Requirements for Expanded Access Record described in 42 CFR 11.28(c)
  - Responsible Party is both the manufacturer of the investigational drug product and the sponsor of the ACT
  - Generally, only one expanded access record for each investigational drug product
  - Similar registration information categories as in 42 CFR 11.28(a), but limited set of data elements based on relevance
    - Fewer data elements required when only "individual patient" expanded access
  - Expanded Access Type * (new)
    - Individual patient
    - Intermediate
    - Treatment use

* Newly required by the final rule
Final Rule Section IV.B.4. What constitutes clinical trial registration information? - § 11.28 (81 FR 65032 - 62)

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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))
Final Rule Section IV.C.4. What constitutes clinical trial registration information? - § 11.28 (81 FR 65032 - 62)

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Protocol and Statistical Analysis Plan

- Part of clinical trial results information
  - Will be posted publicly as described in 42 CFR 11.52
- 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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Redaction and Protocols

- The responsible party may redact personally identifiable information and trade secret and/or confidential commercial information
- The burden of redacting protocols prior to submission is on the responsible party; the Agency does not intend to review protocols to assess whether they contain trade secret and/or confidential commercial information.
- The Agency may contact a responsible party if it appears that the responsible party has redacted information that is otherwise required to be submitted under these regulations. More specific guidance regarding redaction will be considered in the future.

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Final Rule Section III.D. Submission of Protocols and Statistical Analysis Plans (81 FR 64999 - 65002)

Which trials must submit clinical trial results information? (42 CFR 11.42)

- Applicable clinical trials for which the studied product is approved, licensed, or cleared by FDA and required to register
  - Primary Completion Date on or after January 18, 2017: 42 CFR 11.48
  - Primary Completion Date before January 18, 2017: STATUTE (FDAAA)
- Applicable clinical trials for which the studied product is **not** approved, licensed, or cleared by FDA and required to register
  - Primary Completion Date on or after January 18, 2017: 42 CFR 11.48
  - Primary Completion Date before January 18, 2017: Not required

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Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48 (81 FR 65079 – 65102)

Final Rule Results Submission Deadlines

- Primary Completion Date on or after January 18, 2017 (Final Rule)
- **Standard submission deadline**
  - Results information must be submitted no later than 1 year after the Primary Completion Date
- Delayed submission of results with certification if seeking initial approval, licensure, or clearance
  - Product not approved, licensed, or cleared by FDA for any use before the Primary Completion Date
  - Sponsor intends to continue with product development and is seeking or intends to seek FDA approval, license, or clearance

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Final Rule Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

Results Submission Deadlines – Initial Approval

- Deadline for submitting results information if delayed with certification for seeking initial approval, licensure, or clearance
  - 30 calendar days after the earlier of the date on which:
    - FDA approves, licenses, or clears the drug, biological, or device product
    - The marketing application or premarket notification is withdrawn without resubmission for not less than 210 calendar days
  - Two-year limitation:
    - Results information must be submitted not later than 2 years after the date on which the certification was submitted (i.e., up to 3 years after the Primary Completion Date)

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Final Rule Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

Implications for "Certify Initial Approval"

- Certify Initial Approval submitted for an applicable clinical trial with a Primary Completion Date before January 18, 2017
  - Submission of the Certify Initial Approval is not required by the statute (FDAAA)
  - Current definition indicates that a studied product was not approved, licensed, or cleared by the FDA for any use by the PCD
  - Results are not required to be submitted (even if product approved at a later date)
  - Note: If results were submitted for such trials, not considered to be a voluntary submission under § 11.60

Final Rule, Section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in This Part. (81 FR 65118 – 22)
ClinicalTrials.gov "Basic Results" Data Element Definitions (DRAFT) April 2015: https://prsinfo.clinicaltrials.gov/results_definitions.html

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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")

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Final Rule Section IV.B.5. By when will the NIH Director post clinical trial registration information submitted under § 11.28? § 11.35 (81 FR 65062 - 64)

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

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

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

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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)

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

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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)

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 Study Start Date (registration) Primary Completion Date (results) ≥ Jan 18, 2017)
- April 18, 2017: Compliance Date
  - Results data elements newly required by final rule will have ERRORS if not completed (if Study Start Date (registration) Primary Completion Date (results) ≥ Jan 18, 2017)

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

PRS Update – October 22nd

- Upcoming PRS release on PRS (Oct 22nd)
- Optional data elements for submitting results information
  - Study designs in which the unit of assignment or unit of analysis is other than participants; new options for providing other units in Participant Flow and Baseline Characteristics
  - New options for specifying a number that is a "count"
  - New options for different types of "row" data
  - New "product issues" option in Organ System Class (MedDRA v. 19.0)
- New API option for downloading information from the PRS

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Additional Resources

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

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
- Final Rule Information: https://prsinfo.clinicaltrials.gov
  - Sign-up for NIH FDAAA Update listserv to receive notification when new information is added
- Questions: register@clinicaltrials.gov

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