

# ClinicalTrials.gov Requirements

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# What is ClinicalTrials.gov?

- ClinicalTrials.gov is a registry and results information database of publicly and privately supported clinical studies of human participants conducted around the world.
- Established under the Food and Drug Administration Modernization Act of 1997 (FDAMA)
- Expanded under the Food and Drug Administration Amendments Act of 2007 (FDAAA)
- Primary responsibilities under Title VIII, FDAAA are split
  - NIH has implementation responsibilities
  - FDA has compliance and enforcement responsibilities



# ClinicalTrials.gov Final Rule Timeline

- Final Rule (42 CFR Part 11) issued: September 21, 2016
- Effective Date: January 18, 2017
- Compliance Date: April 18, 2017

# Definitions in Final Rule

- Applicable clinical trial [42 CFR 11.10]
  - Not all trials are applicable clinical trials
  
- Applicable drug clinical trial
  1. Controlled clinical investigation
    - other than a phase I
    - drug subject to section 505, FD&C Act or section 351, PHS Act; or
  
  2. Clinical trial of combination product with drug PMOA meeting all other requirements in item 1. above

**Note:** All interventional trials considered controlled for purposes of 42 CFR Part 11

# Definitions in Final Rule

- Applicable device clinical trial
  1. Prospective clinical study of health outcomes
    - comparing an intervention with a device product subject to section 510(k), 515, or 520(m), FD&C 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 devices products where the primary outcome measure relates to feasibility and not to health outcomes;
  2. Clinical trial of combination product with device PMOA meeting all other requirements in item 1. above; or
  3. Pediatric postmarket surveillance of a device product required under section 522.

## Definitions in Final Rule

- Responsible Party [42 CFR 11.10]
  - Sponsor of the clinical trial (as defined at 21 CFR 50.3); or
  
  - Principal investigator of the clinical trial; if
  - Designated by sponsor, grantee, contractor, or awardee, so long as
    1. PI responsible for conducting the trial,
    2. Has access to and control over the data,
    3. Has the right to publish the results of the trial, and
    4. Has the ability to meet all of the requirements for the submission of clinical trial information.

# Clinical Trial Registration

- Clinical Trial Registration
  - Required to register within 21 days of first human subject enrolled [42 CFR 11.24]
  - Registration data elements:
    - Descriptive information
    - Recruitment information
    - Location and contact information
    - Administrative data
  - Subject to quality control [42 CFR 11.64(b)]
    - Correct or address issues within 15 days of electronic notification

# Results Information Reporting

- Clinical Trial Results Information

Results information data elements:

- Participant flow
- Demographic and baseline characteristics
- Outcomes and statistical analyses
- Adverse event information
- Protocol and statistical analysis plan
- Administrative information



# Results Information Reporting

- All applicable clinical trials subject to the final rule requirements are required to submit results information
- Results information *generally* due 12 months after primary completion date of the applicable clinical trial.
- Submission of results information may be delayed with certification
  - for a trial seeking initial approval, licensure, or clearance
  - for a trial seeking approval, licensure, or clearance of a new use
- Results information may not be due for up to three years
- Must submit copy of protocol and statistical analysis plan

# Updating Requirements

- ClinicalTrials.gov record must be updated
  - at least every 12 months
  - certain data elements, within 30 days
    - Expanded Access Information
    - Overall Recruitment Status
    - Study Start Date
    - Individual Site Status
    - Human Subjects Protection Review Board Status
    - Primary Completion Date
  - certain data elements, within 15 days
    - Device Product Not Approved or Cleared by U.S. FDA

# Related FDA Requirements

In addition to requirements under 42 CFR Part 11:

- Certification of Compliance with ClinicalTrials.gov requirements
  - Form FDA 3674
  - Guidance <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm>
- Informed Consent Documents and Processes (21 C.F.R. § 50.25(c) Mandatory Statement)
  - “A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”
  - Guidance <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf>
- Periodic Reports on Postmarketing Requirements
  - Section 505(o)(3)(E) of the FD&C Act

# Potential Legal Consequences of Non-compliance

## Explained in 42 CFR 11.66:

- Civil or criminal judicial actions for prohibited acts
  - Failure to submit a certification required by 402(j)(5)(B) of the PHS Act or knowingly submitting a false certification
  - Failure to submit clinical trial information
  - Submission of clinical trial information which is false or misleading in any particular
- Civil monetary penalties (amounts adjusted going forward)
  - Up to \$11,569 for all violations adjudicated in a single proceeding
  - Up to \$11,569/day for each day if not corrected within 30 days after notice of noncompliance
- Grant funding actions
  - HHS Grant progress report - Certification that all required clinical trial information has been submitted
  - If not verified that clinical trial information has been submitted:
    - Remaining grant funding or funding for future grant not released to grantee

# FDA Compliance/Enforcement Activities Post Final Rule

## Compliance/enforcement activities:

- Incorporated into FDA's existing compliance program structure
- Part of FDA's Bioresearch Monitoring Program (BIMO)
- Encourage compliance with ClinicalTrials.gov requirements similar to how FDA encourages compliance with other statutory provisions
- FDA and NIH will work together to ensure compliance and enforcement activities are carried out in a coordinated fashion

# FDA Compliance/Enforcement Activities

Information that may be evaluated in the process of considering whether to take action:

- ClinicalTrials.gov individual NCT record, including archived information
- Information collected as part of an FDA inspection
- Other ClinicalTrials.gov NIH/NLM records – such as submissions not yet posted, including results data and non-public information
- Related Publications – Journal Articles, Conference Materials
- Media Articles

# FDA Compliance/Enforcement Activities

- Future compliance/enforcement actions will require extensive analysis of existing public and non-public data to determine action
- Potential noncompliance assessed on case-by-case basis
- No civil monetary penalties assessed to date
- Conducted pilot enforcement project
  - Help development of comprehensive enforcement program
  - 15 Pre-Notice of Noncompliance Letters sent
  - All parties complied with law after receiving a Pre-Notice

# Other Clinical Trial Reporting Requirements

- NIH Policy on Dissemination of NIH-Funded Clinical Trial Information<sup>1</sup>
  - All NIH-funded clinical trials must be registered and submit results to ClinicalTrials.gov
  - Clinical Trial means “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”
  - Includes phase 1 drug trials, device feasibility studies and any intervention not regulated by FDA
- International Committee of Medical Journal Editors (ICMJE)<sup>2</sup>
  - Recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.

1. See 81 FR 64922

2. See <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>



# FDA Draft Guidance: Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank (September 2018)

Intended to address the following questions:

- How do the Centers intend to identify whether responsible parties have failed to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank or submitted false or misleading information to the data bank, or whether submitters have failed to submit to FDA the certification required by section 402(j)(5)(B) of the PHS Act or knowingly submitted a false certification to FDA?
- Under what circumstances may a Center decide to seek civil money penalties against a responsible party or submitter?
- What procedures apply when a Center seeks civil money penalties?
- What civil money penalty amounts may be assessed?

# Resources

ClinicalTrials.gov Final Rule (42 CFR part 11)

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

Statutory language of Title VIII of FDAAA

<http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82>

Form FDA 3674

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf>

FDA Guidance on Form FDA 3674

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm>

FDA Guidance on Informed Consent Element at 21 CFR 50.25(c)

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf>

# Resources

NIH Information on 42 CFR Part 11

<https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public>

NIH Clinical Research Policy Page

<http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials>

ClinicalTrials.gov Website

<https://clinicaltrials.gov/>

NIH ClinicalTrials.gov Training Materials

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

FDA Draft Guidance on Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

<https://www.fda.gov/RegulatoryInformation/Guidances/ucm607652.htm>



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