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ClinicalTrials.gov Reporting: NIH Policy & HHS Final Rule

Federal Demonstration Partnership Meeting – January 2017

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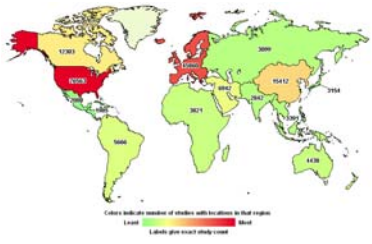
NIH U.S. National Library of Medicine https://ClinicalTrials.gov

About ClinicalTrials.gov

- Clinical studies registry and results database
  - Over 233,000 studies (interventional & observational studies)
  - Studies with locations in 50 states and 191 countries
  - Privately and publicly funded studies involving human subjects
  - Study information submitted by sponsor or principal investigator
- Website and registry launched in February 2000
  - Results database launched September 2008
  - Over 23,000 studies with results
- Database updated nightly
- Usage
  - 200 million page views per month
  - 65,000 visitors per day



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Brief History - Select U.S. Laws and Policies

- **1997 Food and Drug Administration Modernization Act (FDAMA)**
- 2000 ClinicalTrials.gov launched
- **2005 International Committee of Medical Journal Editors (ICMJE)**
- **2007 Food and Drug Administration Amendments Act (FDAAA)**
- 2008 FDAAA results submission requirements start
- 2013 Centers for Medicare & Medicaid Services (CMS)
- 2014 FDAAA Notice of Proposed Rulemaking (NPRM) and National Institutes of Health (NIH) Policy Proposal
- **2016 Final Rule for FDAAA (42 CFR Part 11) and NIH Policy on Dissemination of Clinical Trial Information**

https://clinicaltrials.gov/ct/manage-recs/resources

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Why Register and Report Results?

- **Required by most medical journals (ICMJE)**
  - Registration for all clinical trials (all interventions)
- **Federal law (FDAAA 801) and regulations (42 CFR Part 11)**
  - Registration & results submission for "applicable clinical trials"
- **Expectation for all NIH-supported clinical trials**
  - Registration & results submission, even if not subject to FDAAA 801
  - Note: NCI previously established a results policy (effective 1/8/2015)

ICMJE = International Committee of Medical Journal Editors; FDAAA 801 = Section 801 of the Food and Drug Administration Amendments Act of 2007; NIH = National Institutes of Health; NCI = National Cancer Institute

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General Requirements – Final Rule & FDAAA

The Responsible Party for an Applicable Clinical Trial (ACT) must:

1. **Register** the trial in ClinicalTrials.gov no later than 21 days after enrollment of the first participant
2. **Update** the trial in ClinicalTrials.gov at least once every 12 months (some information within 15 or 30 days of change*)
3. **Submit summary results** (including adverse events) for certain trials not later than 1 year after the trial's Primary Completion Date
   - Delays allowed in some circumstances

Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11);
* Update requirements described in 42 CFR 11.64

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General Requirements - NIH Policy

- "For those covered by the NIH policy only, NIH-funded awardees and investigators will be expected to submit the same registration and results information in the same timeframes as those subject to the statute and rule"

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

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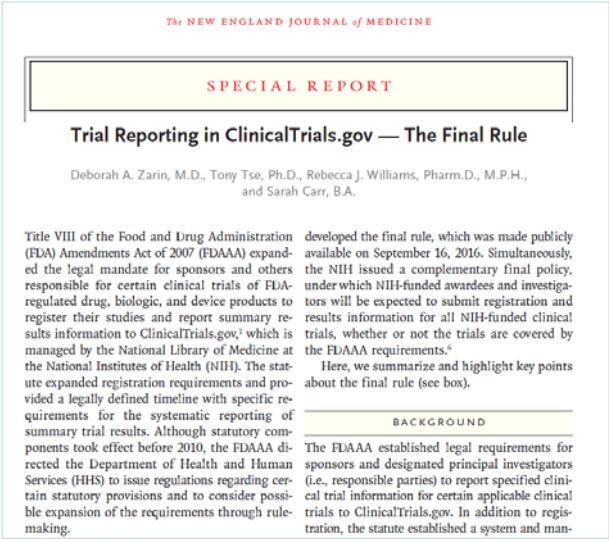
Overview of the Final Rule



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,[1] 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.[6]

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-

- Clarifies terms and provisions in the statute (FDAAA)
  - ACT determination approach
- Expands basic requirements
  - Results information required for ACTs of unapproved products
  - Full protocol and statistical analysis plan required with results (will be made public)
- Other Issues
  - Narrative summaries not required

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Zarin et al. N Engl J Med; 2016 Sept 16.

Determination of an Applicable Clinical Trial

See also complete definition of Applicable Clinical Trial (42 CFR 11.10)

For a study initiated on or after January 18, 2017 (42 CFR 11.22):

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

* 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 (42 CFR 11.22(b))
IND = Investigational New Drug application; IDE = Investigational Device Exemption

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Clinical Trial Information: FDAAA v. Final Rule

- FDAAA enacted - September 27, 2007
  - Study Start Date before Jan 18, 2017: FDAAA registration requirements
  - Primary Completion Date before Jan 18, 2017: FDAAA results requirements (excludes ACTs of products not previously approved or cleared by FDA)
- Final Rule Published - September 21, 2016
- Final Rule Effective Date - January 18, 2017
  - Study Start Date on or after Jan 18, 2017: Final rule registration requirements
  - Primary Completion Date on or after Jan 18, 2017: Final rule results requirements (includes ACTs of products not previously approved or cleared by FDA)
- Compliance date - April 18, 2017 (90 days after effective date)

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

Overview of Implementation Plans

- November 30, 2016: New registration and results final rule-related data elements released to the Test Protocol Registration and Results System (PRSTest; https://prstest.nlm.nih.gov)
- January 18, 2017: Effective Date
  - Release will be operational on PRS; data elements newly required by the final rule will be available and have a WARNING if not completed (based on Study Start Date & Primary Completion Date)
- April 18, 2017: Compliance Date
  - Data elements newly required by the final rule will have ERRORS if not completed (based on Study Start Date & Primary Completion Date)

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See https://prsinfo.clinicaltrials.gov

Prior to Trial Initiation

- Identify the Responsible Party
  - Sponsor (only one)
    - IND or IDE holder; if none, then person or entity who "initiates" the trial
      - Funding recipient if grant or sponsored research agreement
      - Funder if procurement funding agreement (contract)
  - Sponsor may designate the Principal Investigator (PI) as Responsible Party if PI meets certain requirements
    - Is responsible for conducting the trial;
    - Has access to and control over the data from the trial;
    - Has the right to publish the results of the trial; and
    - Has the ability to meet all of the requirements for submitting and updating clinical trial information

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42 CFR 11.4; IND/IDE= Investigational New Drug Application/Investigational Device Exemption

Register the Clinical Trial

- Timing of registration requirement
  - Before 1st participant is enrolled (**ICMJE**)
  - Within 21 days of 1st participant being enrolled (**FDAAA/Final Rule**)
  - Tip: Enter NIH Grant number in study record (Secondary ID)
- Informed Consent
  - FDA regulations require a statement to be included in informed consent documents of applicable clinical trials regarding availability of information at ClinicalTrials.gov (21 CFR 50.25(c))
  - NIH Policy also requires similar statement

21 CFR 50.25(c): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25
FDA Guidance: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf

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Update Clinical Trial Information

- Responsible Party must update and correct clinical trial information on ClinicalTrials.gov
  - Generally required to update information at least once every 12 months
  - Some data elements must be updated more rapidly
    - FDAAA – Overall Recruitment Status and Primary Completion Date within 30 days
    - Final Rule – Additional data elements must be updated within 15 or 30 days of a change
  - Corrections may be required if potential issues identified as part of ClinicalTrials.gov quality control review or responsible party becomes aware of errors

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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)

Submit Clinical Trial Results Information

- Standard results submission deadline
  - 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
  - Seeking initial approval, licensure, or clearance
  - Extensions for good cause

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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)

Key Definition

- Primary Completion Date
  - The date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
  - In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

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Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10 (81 FR 65025 – 6)

Clinical Trial Results Information: Final Rule

- Scientific Information ("per arm")
  - Participant Flow
  - Demographic and Baseline Characteristics
  - Primary and Secondary Outcome Measures and Statistical Analyses
  - Adverse Event Information
  - Protocol and Statistical Analysis Plan
- Administrative Information
  - Results Point of Contact
  - Certain Agreements (related to investigator's right to publish, if not an employee of sponsor)

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Final Rule Section IV.C.4. What constitutes clinical trial results information? - § 11.48(a) (81 FR 65079 - 101)

General Results Clarifications

- Summary results at the end of the trial
  - No interim or "real-time" reporting
  - No participant-level reporting
- Summary results submission generally not required for:
  - Registered non-ACTs (e.g., observational, Phase 1)
  - Clinical trials completed by December 26, 2007
  - ACTs of products that are not approved as of the Primary Completion Date (PCD), when the PCD is before January 18, 2017 (final rule effective date)
- Relationship to publication (ICMJE)
  - Submitting summary results to ClinicalTrials.gov will not interfere with publication* (but, failing to register the trial will!)

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* http://www.icmje.org/publishing_10register.html

Other Considerations

- Certification of Compliance to FDA
  - Form 3674 accompanies drug, biological, and device product submissions
- Certification of Compliance to NIH
  - NIH grantees must certify compliance in applications and progress reports
- CMS Coverage for Routine Costs in Clinical Trials (as of Jan 1, 2015)
  - Must provide NCT number if submitting claims for clinical trial routine costs
- FDA Compliance Program 7348.810
  - Instructs FDA staff to identify SOPs and determine if studies reported to ClinicalTrials.gov appropriately

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Support Materials: http://www.clinicaltrials.gov/ct2/manage-recs/resources

Potential Consequences of Non-Compliance

- NIH (or other HHS agency) must verify submission of information before releasing any remaining funds for a grant or funds for a future grant and provide opportunity to remedy
- FDA may provide responsible parties with a Notice of Noncompliance and allow 30 days to remedy
- FDA authorized to assess civil monetary penalties up to $10,000/day (amounts adjusted going forward)
- FDA may initiate civil or criminal proceedings
- Notices of non-compliance included in the public record

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Final Rule Section IV. E.1. What are the potential legal consequences of not complying with the requirements of this part? - § 11.66

STAT News – December 13, 2015

- Assessed whether institutions reported results and whether they were reported "on time"
  - Analysis included trials of unapproved drugs or devices, if a certification was not on file
- "The worst offenders included four of the top 10 recipients of federal medical research funding from the National Institutes of Health: Stanford, the University of Pennsylvania, the University of Pittsburgh, and the University of California, San Diego."

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http://www.statnews.com/2015/12/13/clinical-trials-investigation/

Tips: Take a Team Approach

- Be aware of your institution's approach/SOP
- Work as a team to identify Responsible Party and trials to be reported
  - Sponsored research office, Principal Investigator, Counsel
  - Work across institutions
  - Take actions early to clarify roles and responsibilities
- Create a culture of disclosure

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Tips: Manage Risk Wisely

- Grantee Institutions as Sponsors
  - Standard operating procedures
    - Including addressing when key personnel leave the institution
  - Training
  - Monitor compliance
    - How will you identify and track trials that must be registered and have results submitted?
    - (Some institutions require NCT number for IRB approval)
  - Use personnel and resources appropriately
    - Plan for registration and results reporting early in the trial development process
  - Implement appropriate record retention

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NIH Grants FAQs: http://grants.nih.gov/Clinicaltrials_fdaaa/faq.htm

Final Rule Webinar Series

- Available at: http://clinicaltrials.gov/ct2/manage-recs/present

1. Overview of the Final Rule – effective and compliance dates, applicability of final rule, and results submission for unapproved products
2. Final Rule Clinical Trial Registration Information Submission Requirements - who, when, what, and update requirements
3. Final Rule Clinical Trial Results Information Submission Requirements - who, when, what, update requirements, posting, & quality control

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Public Benefits of Access to Clinical Trial Data

- Meet ethical obligation to human subjects (i.e., that results will be used to help others/inform science)
- Inform future research and research funding decisions
- Mitigate information bias (e.g., non-publication)
- Evaluate research integrity (e.g., adherence to protocol)
- Prevent duplication of trials of unsafe or ineffective interventions
- Provide access to data to support evidence-based medicine
- Enhance patient access to enrollment in clinical trials

All contribute to increased public trust in clinical research

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Additional Resources

International Committee of Medical Journal Editors (ICMJE) Policy
http://www.icmje.org/publishing_10register.html

HHS Final Rule Clinical Trials Registration and Results Information Submission
https://www.federalregister.gov/d/2016-22129

NIH Policy on the Dissemination of Clinical Trial Information
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

National Cancer Institute (NCI) Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials
http://grants.nih.gov/grants/guide/notice-files/NOT-CA-15-011.html

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Additional Resources (cont.)

Contact us: register@clinicaltrials.gov

Final Rule Information
https://prsinfo.clinicaltrials.gov

ClinicalTrials.gov Information (Submit Studies page)
https://clinicaltrials.gov/ct2/manage-recs

Office of Extramural Research (OER)
http://grants.nih.gov/Clinicaltrials_fdaaa/

Food and Drug Administration (FDA)
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm

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Select Publications

Available at: http://www.clinicaltrials.gov/ct2/resources/pubs

Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. N Engl J Med; 2016 Sept 16.

Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. JAMA; 2016 Oct 4;316(13):1353-1354.

Zarin DA, Tse T, Ross JS. Trial-results reporting and academic medical centers. *N Engl J Med*. 2015 May 20.

Tse T, Williams RJ, Zarin DA. Reporting basic results in ClinicalTrials.gov. *Chest* 2009;136:295-303.

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