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Final Rule and NIH Policy for Clinical Trials Registration and Results Information Submission

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Agenda

- ClinicalTrials.gov
  - Background and current requirements
- Final Rule
  - General information
  - New data elements and requirements
- NIH Policy
- Consent Form Requirements
- ICMJE Recommendations
- Q&A

Terms and Acronyms

Acronym	Expansion
CFR	Code of Federal Regulations
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
HHS	(U.S. Department of) Health and Human Services
ICMJE	International Committee of Medical Journal Editors
NIH	(U.S.) National Institutes of Health
PRS	Protocol Registration and Results System

ClinicalTrials.gov – What Is It?

- Registry of federally and privately supported research studies conducted in the United States and around the world.
- Web-based resource that provides patients, family members, health care professionals, researchers and the public with easy access to information on clinical studies.
- Free service of the NIH, developed by the National Library of Medicine (NLM).

ClinicalTrials.gov – Why Register?

- Federal Regulations
  - Food and Drug Administration Modernization Act of 1997 (FDAMA)
  - Food and Drug Administration Amendments Act of 2007 (FDAAA)
    - U.S. Public Law 110-85, Title VII (also known as FDAAA 801)
  - Final Rule NEW (42 CFR Part 11)(2016)
- NIH Policy NEW on the Dissemination of NIH-Funded Clinical Trial Information (2016)
- ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (2005)
- Promotes transparency to the public about clinical trials
- Assists in enrollment

Which Trials Must Be Registered and Have Results Submitted to ClinicalTrials.gov?

“Applicable Clinical Trial” (ACT) includes:

- Phase 2,3 and 4 interventional studies;
- Controlled clinical studies involving drugs, biological products and medical devices regulated by the FDA;

  and

- Studies having at least one site in the United States or one of its territories, investigate a product manufactured in and exported from the U.S., *or* are conducted under an Investigational New Drug (IND) or Investigational Device Exemption (IDE).

Exclusions to the Definition of an ACT

Trials that are not required to be registered include:

- Phase 1 (drug) or small feasibility (devices) trials
- Behavioral interventions (no drug, biologic or device involved)
- Observational studies (non-interventional)
- Trials that are ongoing as of September 2007 and reached their completion before December 2007

ClinicalTrials.gov Protocol Data Elements

Registration Information

- Descriptive information about the trial
- Recruitment information
- Location and contact information
- Administrative data

Results Information

- Participant flow and baseline characteristics (e.g., demographics) of the study population
- Outcomes measures and statistical analyses
- Adverse events
- Administrative information (e.g., study results point of contact)

Final Rule: Purpose

- Aims to increase the availability of information to the public about clinical trials – information that is not systematically available from other public sources
- Encourages compliance with current regulations and registration requirements
- Clarifies and expands the legal mandate for sponsors and others responsible for certain clinical trials to register their studies and report summary results information to ClinicalTrials.gov

Final Rule: Overview

Released Date: September 16, 2016
Effective Date: January 18, 2017
Compliance Date: April 18, 2017

- Applies, in general, to “responsible parties” for ACTs
- Covers all clinical trials that are currently subject to FDAAA 801
- The Final Rule does not change the legal definition of an ACT but clarifies which trial information is mandatory for submission.

  Examples include:

  – All interventional studies with pre-specified outcome measures, including those with one intervention group are considered to be “controlled” investigations

  – Phase 1/Phase 2 trials are considered to be Phase 2 trials

Final Rule: Timeline

- **November 30, 2016** – Some of the new data elements specified in the final rule have been added to the PRS Test System to help responsible parties better understand the new elements and requirements.
- **January 18, 2017** (effective date) – The new data elements will be available in the operational PRS, but will not be required by the PRS.
- **April 18, 2017** (compliance date) – Submission of the new ("expanded") data elements will be required in the PRS for the following trials:
  - "Expanded" registration information: Applicable clinical trials with a Study Start Date that is on or after the effective date, January 18, 2017.
  - "Expanded" results information: Applicable clinical trials with a Primary Completion Date that is on or after the effective date, January 18, 2017.

https://prstest.nlm.nih.gov

Which ACTs are subject to the Final Rule?

- It is important to look at both the study start date and primary completion date when determining which requirements apply to a record.

FDAAA	Final Rule
	January 18, 2017
	● Study Start Date on or after 1/18/2017
	Final Rule registration information requirements apply
	● Primary Completion Date on or after 1/18/2017
	Final Rule results information requirements apply

- Example: If the study start date for a trial is June 2014 but the primary completion date is July 2017, registration information will follow FDAAA regulations, but results information will follow the Final Rule.

Final Rule: Compliance

- Notice of Noncompliance (FDA)
- Civil monetary penalties (e.g., up to $10,000 per day)
- Injunction action or criminal prosecution
- Jeopardy to grant funding and future funding
- Identification of clinical trial record as non-compliant in ClinicalTrials.gov

Changes from Current Practice Described in the Final Rule – Registration Information

- The Final Rule clarifies and expands requirements for submitting information to ClinicalTrials.gov under FDAAA 801.
- New ("expanded") data elements and existing optional data elements will be required for submission in the PRS by the Final Rule.
- Submitted information will be posted on ClinicalTrials.gov within 30 days after receipt, even if there are outstanding issues with the quality-control review.
  - Records that do not meet the review criteria will be returned with comments and/or a disclaimer (a general explanation of the concerns about quality).
  - Registry submissions will not be assigned an NCT number until the quality criteria are met.

Final Rule: Data Fields

Current PRS System

* Required by ClinicalTrials.gov

‡ = FDAAA Required to comply with US FDA Amendments Act

(‡) = (FDAAA) May be required to comply with US FDA Amendments Act

Updated PRS System (January 18, 2017 and on)

* Required

* § Required if Study Start Date is on or after January 18, 2017

[*] Conditionally required (see Definitions)

Clinical Trial Registration Information (1)

- Study Identification
  - Official Title
  - Secondary IDs and ID Type - including unique identifiers from NIH grant numbers, if applicable
- Study Status
  - Overall Recruitment Status
  - Why Study Stopped, if terminated, withdrawn, suspended
  - Study Start Date
  - Study Completion Date
  - Expanded Access Status - indicating current availability status

Clinical Trial Registration Information (2)

- Sponsors/Collaborators
  - Responsible Party Contact Information **NEW – not disclosed to the public**
- Oversight
  - 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 **NEW**
  - Product Manufactured in and Exported from the U.S. **NEW**
  - Pediatric Post-market Surveillance of a Device Product **NEW**

Clinical Trial Registration Information (3)

- Study Design (All sub-elements)
  - Expanded Access Type NEW - individual patient, intermediate, treatment use
  - Primary Purpose NEW - dropdown option: device feasibility
  - Enrollment
- Arms and Interventions
  - Other Names (used to identify the intervention), if any
  - Intervention Description
- Outcome Measures
  - Primary Outcome Measure (POM) Description
  - Secondary Outcome Measure (SOM) Description
- Eligibility
  - Accepts Healthy Volunteers

Clinical Trial Registration Information (3)

- Study Design (All sub-elements)
  - Expanded Access Type NEW - individual patient, intermediate, treatment use
  - Primary Purpose NEW - dropdown option: device feasibility
  - Enrollment
- Arms and Interventions
  - Other Names (used to identify the intervention), if any
  - Intervention Description
- Outcome Measures
  - Primary Outcome Measure (POM) Description
  - Secondary Outcome Measure (SOM) Description
- Eligibility
  - Accepts Healthy Volunteers

Final Rule – Results Information

- Final Rule only applies to an ACT with a primary completion date on or after the effective date, January 18, 2017, of the Final Rule.
- Summary results information is now required to be submitted for any ACT, regardless of whether the drug, biological, or device product have been approved, licensed, or cleared for marketing by the FDA.
- Results submission can be delayed for as long as 2 additional years if the Responsible Party submits a certification to ClinicalTrials.gov
  - Product is not approved, licensed or cleared for marketing and is still under development; or
  - Manufacturer is the sponsor of the clinical trial and will seek approval, licensure, or clearance for a new use within 1 year.
- Clarifies that certain exploratory or other outcome measures for which there are no prespecified analytic plans are not considered “secondary”

Final Rule – New Requirements

- New ("expanded") data elements and existing optional data elements will be required in the PRS by the Final Rule.
- Adds a third table for summarizing all-cause mortality, with number and frequency of deaths due to any cause by arm
- Adds a requirements to submit the clinical trial protocol and statistical analysis plan (SAP) at the time of results information submission.
  - PHI and trade secret(s) and/or confidential commercial information can be redacted unless the information is required to be submitted by the regulation.
  - Must include all amendments that have been approved by a human subjects protection review board in a specified common electronic document format (e.g., PDF).
- Submitted information will be posted on ClinicalTrials.gov within 30 days after receipt, even if there are outstanding issues with the quality-control review.

Final Rule – Results Reporting Deadlines

- In general, results information must be submitted no later than 1 year after the primary completion date of an ACT.
- While the Final Rule does not change the standard deadline for reporting primary outcome measure data, it does establish deadlines for submitting results information for secondary outcome measures and/or adverse event information that have not been collected by the Primary Completion Date.

Type of Results Information	Deadline
Primary Outcome Measure	Up to 1 year from the primary completion date
Secondary Outcome Measure	Up to 1 year from the study completion date new
Adverse Event (AE) Information	Up to 1 year after date of AE data collection new

Clinical Trial Results Information (1)

- Participant Flow
  - Arm/Group Title and Description §
  - Pre-Assignment Details, in any
  - Participant Data NEW - description of the unit of assignment, if other than ‘participants’, and number of units that started and completed the clinical trial, by arm

Clinical Trial Results Information (2)

- Baseline Characteristics
  - Arm/Group Title and Description §
  - Overall Number of Units Analyzed NEW - if unit is other than 'participants'
  - Analysis Population Description
  - Race and Ethnicity §, if collected under protocol
  - Other measures assessed at baseline and used in the analysis of POM
  - Measure Type and Measure of Dispersion NEW - dropdown option: count of participants, count of units, and geometric least squares mean
  - Number of Baseline Participants (and Units) NEW - if unit is other than 'participants'

Clinical Trial Results Information (3)

- Outcome Measures
  - Arm/Group Title and Description
  - Analysis Population Description
  - Outcome Measure Description § (metric used to characterize specific outcome measure)
  - Type of statistical test conducted - superiority, non-inferiority, equivalence, or other NEW
- Adverse Events
  - Time Frame §
  - Additional Description (e.g., different definition of AE/SAE)
  - Assessment Type - collection approach § (whether systematic or non-systematic)
  - Arm/Group Title and Description §
  - All-cause mortality § NEW
  - Organ system - new dropdown menu option: product issues

Update Requirements

	Trials initiated before January 18, 2017 (FDAAA)	Trials initiated after January 18, 2017 (Final Rule)
General updates	Once per year	Once per year
15 calendar day updates	N/A	Only for a change in the approval or clearance status of a device product not approved or cleared by the FDA
30 calendar day updates	Any change in the following: • Overall recruitment status • Primary completion date	Any change in the following: • Study start date • Intervention name • Availability of expanded access • Overall recruitment status • Individual site status • IRB review status • Primary completion date • Study completion date • Responsible Party (RP) • Contact for RP
Comments (errors, deficiencies and/or inconsistencies identified) related to registration information	N/A	Correct or address within 15 calendar days
Comments (errors, deficiencies and/or inconsistencies identified) related to results information	N/A	Correct or address within 25 calendar days

NIH Policy: Purpose

- Promotes broad and responsible dissemination of information from NIH-funded clinical trials to the research community and to the public at large
- Expects all NIH-funded awardees and investigators to register and submit summary results, including adverse event information, to ClinicalTrials.gov in the same timeframes as trials subject to Final Rule
- Makes results and accomplishments of research activities available to inform future research and to increase public trust

Scope of the NIH Policy

- Applies to clinical trials which are defined as:

  "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."

- Applicants for NIH funding are required to submit a plan outlining how they will comply with the expectations of the policy.
- Applies to applications and proposals received and clinical trials submitted for IRB review on or after January 18, 2017.
- Requirements will follow Final Rule.

NIH Policy: Overview

Release Date: September 16, 2016
Effective Date: January 18, 2017

- Applies to **all** NIH-funded awardees and investigators conducting clinical trials funded in whole or in part by the NIH
  - Does not apply to clinical trials that use NIH-supported infrastructure, but receive no other NIH funds for the conduct of a specific clinical trial
- Covers all clinical trials regardless of study phase, type of intervention, or whether subject to FDAAA or the Final Rule
  - Phase 1 trials of drugs and biologics
  - Small feasibility studies of device products
  - Clinical trials of behavioral, surgical, and other types of health and medical interventions

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

NIH Policy: Compliance

- Expectations are included in the terms and conditions of the NIH award
- Noncompliance can result in:
  - Suspension or termination of funding
  - Jeopardy to future funding decisions
  - Identification of clinical trial record as non-compliant in ClinicalTrials.gov
  - Enforcement actions of the Final Rule, if applicable

What are the Informed Consent Requirements Related to ClinicalTrials.gov?

For any clinical trial subject to the Final Rule or NIH Policy, the following statement must be reproduced word for word in the applicable informed consent documents:

"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."

FDA Guidance on informed consent requirements

ICMJE Clinical Trial Registration Policy

- The ICMJE Clinical Trial Registration Policy (2005)
  - Published as part of the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals
  - Followed by more than 1,000 journals
- Journal editors require that all clinical trials be entered in a public registry before the start of participant enrollment as a condition of publication.
- *FDAAA/Final Rule* and ICMJE policies overlap in scope, but the ICMJE policy covers more kinds of trials and intervention types and requires earlier registration. Register **all** interventional studies to meet both ICMJE and FDAAA/Final Rule.

ICMJE Clinical Trial Registration Policy
ICMJE Recommendations in Medical Journals

ICMJE Clinical Trial Registration Policy

- Applies to the World Health Organization (WHO) definition of a clinical trial:

  "Any research study that prospectively assigns human participants or groups of humans to 1 or more health-related interventions to evaluate the effects on health outcomes."

- ICMJE requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials.
- ICMJE will not consider results data that is posted in the tabular format required by ClinicalTrials.gov to be *prior publication*.

Summary Table

Reporting Requirement	Final Rule (Issued in 2016)	NIH Policy (Issued in 2016)	ICMJE
Effective Date	January 18, 2017	January 18, 2017	N/A
Compliance Date	April 18, 2017	N/A	N/A
Scope	Registration and Results Reporting	Registration and Results Reporting	Registration
Phase	Not Phase I	All	All
Intervention Type	Drug, biologic and device products regulated by the FDA	All (e.g., including behavioral interventions)	All
Funding Source	Any	NIH	Any
Registration Deadline	No later than 21 days after enrollment of the first participant	No later than 21 days after enrollment of the first participant	Prior to enrollment of first participant
Results Deadline	No later than 12 months after primary completion date (Delay may be requested)	No later than 12 months after primary completion date (Delay may be requested)	N/A (Encouraged, but not addressed in policy)
Enforcement	• Criminal proceedings and civil penalties (up to $10,000/day) • Loss of funding • Record identified as non-compliant	• Loss of NIH funding • Record identified as non-compliant	Refusal to publish

Resources

- Final Rule Information
- Trial Reporting in ClinicalTrials.gov – The Final Rule, New England Journal of Medicine (NEJM)
- Final Rule Webinar Series, National Library of Medicine (NLM)
- NIH News Release: HHS Takes Steps to Provide Clinical Trials Information to the Public

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